E-filed: May 31, 2007 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS & INTERFERENCES

In re application of:	
VAN VLASSELAER, Peter, *et al.*	Art Unit: 1647
Application Serial. No. 09/747,383	Examiner: SEHARASEYON, Jegatheesan
Filed: December 22, 2000	Atty. Dkt. No: 03102.0011.NPUS01
For: **GAMMA-IFN LIQUID-DROPLET AEROSOL AND METHOD**	

SECOND AMENDED APPEAL BRIEF

I. Real Party in Interest

InterMune, Inc., the assignee of record, is the real party of interest in the application at the time this Brief is being filed.

II. Related Appeals and Interference

There are no related appeals or interference known to Appellants that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 16-23 and 25-28 are present in the application, have been rejected by the Examiner and are on appeal.

Claims 1-15 and 24 have been cancelled.

IV. Status of Amendments

No amendments were filed subsequent to the final rejection.

V. Summary of Claimed Subject Matter

Claim 16 depends on Claim 22. Claim 16 is directed to a liquid droplet aerosol composition of γ-IFN containing at least one million International Units of γ-IFN/ml wherein the potency of said γ-IFN is measured by the stimulation of CD-64 antigen expression or HLA-DR antigen expression in cultured human monocytes. Claim 16 is supported by page 3, lines 5-10; page 4, lines 8-13; page 7, lines 11-13; and page 13, lines 20-23.

Claim 17 depends on Claim 22. Claim 17 recites mannitol as the stabilizing agent of the liquid droplet aerosol composition. Claim 17 is supported by page 3, lines 12-13; page 7, lines 26 and 30-31; and in Table 1.

Claim 18 depends on Claim 17. Claim 18 recites that said mannitol stabilizing agent is present at concentrations of 5-15 mM. Claim 18 is supported by page 3, lines 12-13; page 7, lines 30-31; and in Table 1.

Claim 19 depends on Claim 22. Claim 19 recites polysorbate as the dispersing agent of the liquid droplet aerosol composition. Claim 19 is supported by page 8, lines 1-2 and in Table 1.

Claim 20 depends on Claim 19. Claim 20 recites that said polysorbate dispersing agent is present at concentrations of 50-200 mg/liter weight per cent. Claim 20 is supported by page 8, lines 4-5 and in Table 1.

Claim 21 depends on Claim 22. Claim 21 recites that the aqueous γ-IFN solution has a viscosity at room temperature of less that 2Cp. Claim 21 is supported by page 2, lines 26-27; page 3, lines 31-32; page 8, lines 5-8; and in Table 1.

Claim 22 recites a liquid-droplet aerosol composition formed from an aqueous γ-IFN solution having a known γ-IFN biological activity, and comprising a dispersing agent and a stabilizing agent in an amount effective to stabilize the γ-IFN upon aerosolization, wherein the stabilizing agent consists of a sugar, an alcohol, or an amino acid, wherein

the liquid-droplet aerosol composition has (a) defined-size droplet particles in a selected size range selected from the group consisting of (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, and (v) greater than 10 microns, (b) a γ-IFN biological activity substantially the same as that of the aqueous γ-IFN solution, and (c) a γ-IFN molecular size distribution substantially the same as that of the aqueous γ-IFN solution. Claim 22 is supported by page 2, lines 26-29; page 2 lines 30-32 and page 3, lines 1-3; page 3, lines 30-31; page 3, line 32 through page 4, lines 1-7; page 9, lines 4-8; and page 9, lines 21-23.

Claim 23 depends on Claim 22. Claim 23 recites that in said liquid-droplet aerosol composition of γ-IFN, at least 95% of the droplet particles have a size in the selected size range. Claim 23 is supported by page 6, lines 8-9.

Claim 25 depends on Claim 22. Claim 25 recites that in said liquid-droplet aerosol composition of γ-IFN, at least 80% of the droplet particles have a size in the selected size range. Claim 25 is supported by page 6, lines 8-9.

Claim 26 depends on Claim 22. Claim 26 recites that said liquid-droplet aerosol composition of γ-IFN is formed by placing the aqueous γ-IFN solution against a plate having defined-size openings or pores, and forcing the aqueous γ-IFN solution through the openings or pores.. Claim 26 is supported by page 9, lines 9-13, and page 9, lines 19-21.

Claim 27 depends on Claim 22. Claim 27 recites that in said liquid-droplet aerosol composition of γ-IFN, the droplet particles have a size range of 3-5 microns. Claim 27 is supported by page 2, line 32; page 4, line 4; and page 9, line 5.

Claim 28 depends on Claim 22. Claim 28 recites that in said liquid-droplet aerosol composition of γ-IFN, the droplet particles have a size range of 5-10 microns. Claim 28 is supported by page 2, line 32; page 4, line 4; and page 9, line 5.

VI. Grounds of Rejection to be Reviewed on Appeal

Whether claims 16-23 and 25-28 are unpatentable under 35 U.S.C. 103(a) over Huland in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora.

Whether claims 16-23 and 25-28 are unpatentable under 35 U.S.C. 103(a) over Huland and Jaffe in view of both Debs and Ruskewicz as further evidenced by Nayar or Hora.

Whether claims 16-23 and 25-28 are unpatentable under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention.

VII. Argument

A. Rejection under Sec. 103(a) as obvious over Huland in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora.

The Examiner has rejected Claims 16-23 and 25-28 under 35 U.S.C. 103(a) as allegedly being obvious over Huland in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora. Specifically, the Examiner contends that Ruskewicz teaches the production of aerosol compositions with aerosol droplet particle sizes over the range of 1-12 microns, thus overlapping the aerosol droplet particle size ranges recited in the claims. Further, the Examiner further contends that Debs discloses an aerosol composition of rHuTNF-α which retains rHuTNF-α biological activity after aerosolization, and that the stability of such an aerosol composition of rHuTNF-α toward aerosolization makes obvious the aerosolization stability of any cytokine aerosol composition, specifically any aerosol composition of γ-IFN. Thus, the Examiner cites Debs as teaching or suggesting the retention of "substantially the same biological activity" of γ-IFN aerosol compositions toward aerosolization. Finally, the Examiner contends that Ruskewicz teaches the production of aerosol compositions with aerosol droplet particle sizes over the range of 1-12 microns, thus encompassing the claimed "retention of substantially the same molecular size distribution." To the extent that the Examiner's rejection applies, Appellant respectfully traverses.

None of Huland, Debs, Nayar, and Hora disclose a composition of γ-IFN having the claimed defined particle size range.

At Column 17, lines 58-60, Ruskewicz discloses "an aerosol preferably having a particle size in the range of about 1 to 12 microns, more preferably of about 3.0 to 6.0 microns." However, Ruskewicz does not teach or suggest the claimed particle size range of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns. Each of the claimed particle size ranges has a unique application. For example, Appellants have described the desired droplet particle size of less than 1 micron for treating cystic fibrosis, 1-3 microns for delivery to bronchial sites, and 3-5 microns for administering systemically (see application at page 15, lines 1-7).

The Examiner states that the fact that Ruskewicz discloses an aerosol with a particle size range of about 1 to 12 microns, more preferably of about 3.0 to 6.0 microns, and suggests that other particle sizes may be useful makes obvious a disclosure of an aerosol of discrete droplet particle size ranges as recited in Claim 22. Appellants respectfully disagree.

Claim 22 specifically recites aerosol droplet particle size ranges of (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns. Ruskewicz does not teach or suggest any of the claimed size range, but rather describes a much larger particle size range of about 1 to 12 microns. An aerosol producing particles over such a wide range would, as Appellants' specification suggests, deposit aerosol droplets across the respiratory tract rather than targeting desirable areas. Indeed, as Examiner acknowledges, Ruskewicz suggests that other particle size ranges may be desirable in directing compounds to particular areas of the respiratory tract, but Ruskewicz discloses only one such narrower range of particle sizes- 3.0 to 6.0 microns. Therefore, as Ruskewicz suggests, defining narrower aerosol droplet particle size ranges constitutes a novel invention as such aerosols of defined narrower particle size ranges are able to target drug deposition in desired areas of the respiratory tract. Thus, disclosure of an aerosol of droplet particle sizes covering a wide range of values does not make obvious an invention defining aerosols of more narrowly defined particle size ranges and MPEP § 2144.05 [R-3] is inapplicable here.

The Examiner states that the fact that Ruskewicz teaches "about" the claimed 3-5 microns could be considered as "about 3-6 microns." The Examiner uses hindsight to arbitrarily change the 6 micron size described in Ruskewicz to 5.4 micron, then round off 5.4 micron to 5 micron in order to produce the claimed 5 micron value. A skilled person would not interpret the referenced 3-6 microns as being the same as the claimed 3-5 microns, particularly in view of the fact that Claim 22 has specified 3-5 microns and 5-10 microns as different size ranges.

Neither of the cited references teaches or suggests the claimed particle size ranges, therefore, the combination of the cited references does not produce the claimed defined particle size ranges.

None of the cited references Huland, Debs, Ruskewicz, Nayar or Hora describe an aerosol droplet composition of γ-IFN with retention of substantially similar γ-IFN activity compared with the liquid composition prior to aerosolization. Huland, Ruskewicz, Nayar or Hora does not measure the biologic activity of IFN- γ. Debs merely describes the immunomodulatory effects of aerosolized rMuIFN- γ on rat alveolar macrophage and blood monocyte function. Debs does not measure the IFN- γ biological activity before and after aerosolization. The mere presence of some stimulatory potency in an aerosolized composition does not mean that substantially the same γ-IFN biological activity remains in the aerosol droplets as compared with the formulation prior to aerosolization. The biologically active form of γ-IFN is made up of two monomers held together by a non-covalent bond. **It is known in the art that shear forces and other physico-chemical challenges- such as those encountered during an attempt to aerosolize a liquid γ-IFN solution- are not well tolerated by the molecule** (see Declaration of Peter Van Vlassalaer, filed February 17, 2004). It is important for a therapeutic product to retain substantially the same γ-IFN activity in the aerosol droplets such that potent γ-IFN can be delivered to a patient to achieve a therapeutic effect.

The Examiner also asserts that full biological activity of rHuTNF-α was retained in a condensate after aerosolization in Debs, therefore, the Examiner assumes that the claimed γ-IFN activity of the aerosol compositions is substantially the same as that of

solution The Examiner's assumption is incorrect because rHuTNF-α and γ-IFN are structurally and chemically distinct proteins. **The ability to aerosolize one cytokine (rHuTNF-α) without loss of its activity does not indicate the ability to aerosolize another cytokine (γ-IFN), which tends to monomerization or aggregation, without loss of γ-IFN activity.** Based on Debs' teaching of **rHuTNF-α**, a skilled person would not derive the conclusion that γ-IFN can retains full biological activity after aerosolization.

On the contrary, Appellants have demonstrated in Figure 6 that three aerosolized formulations prepared by Appellants showed substantially the same biological activity as that of the non-aerosolized solution (see Figure 6 and page 13, line 31 through page 14, line 4).

None of the cited references Huland, Debs, Ruskewicz, Nayar or Hora describe a composition of γ-IFN with substantially the same molecular size distribution after aerosolization. None of the cited references disclose a molecular size distribution. The limitation of **substantially the same molecular size distribution in Claim 22 refers to protein size at a molecular level, not droplet particle sizes. It is important to maintain the biologically-active dimer form of γ-IFN after aerosolization.**

The Examiner argues that Ruskewicz teaches retention of substantially the same γ-IFN molecular size distribution. However, Ruskewicz only disclose aerosol particle size, which is in the micron range, and is different from a protein molecular size, which is typically in the range of 0.04-0.07 micron. The Examiner has misunderstood the meaning of aerosol particle size versus molecular size. "Molecular size distribution" refers to molecular properties of the a single protein, γ-IFN protein Figures 7 and 8 show the molecular size distribution of γ-IFN protein, which is clearly different from a particle size distribution. Appellants have demonstrated in Figures 7 and 8 that by protein molecular analysis of the collected aerosol samples, aerosolization of IFN- γ solution has no measurable effect on the molecular size distribution, i.e., the state of dimerization, monomerization or aggregation of the IFN- γ (see Figures 7 and 8 and page 14, lines 21-25).

Accordingly, Appellant respectfully submits that the critical features of the presently claimed invention—the production of aerosol compositions with droplet particle sizes of discrete ranges, the stability of biological activity of the aerosol compositions toward aerosolization, and the retention of the molecular size of γ-IFN—has not been taught or suggested by Huland, and that neither the Ruskewicz or Debs references, nor the Nayar or Hora references, discloses matter which, when taken together, teaches Appellant's claimed γ-IFN aerosol compositions. Appellant respectfully submits that the presently claimed invention is patentably non-obvious over Huland in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora, and requests that the Examiner's rejection of Claims 16-23 and 25-28 under Sec. 103(a) be reversed.

B. Rejection under Sec. 103(a) as obvious over Huland and Jaffe in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora.

The Examiner has rejected Claims 16-23 and 25-28 under 35 U.S.C. 103(a) as allegedly being obvious over Huland and Jaffe in view of both Debs and Ruskewicz, and further evidenced by Nayar or Hora.

As discussed above, Huland, Debs, Ruskewicz, Nayar, and Hora do not render Claims 16-23 and 25-28 obvious. The addition of Jaffe does not cure the deficiency of other references.

Jaffe describes a formulation with a particle size of "0.1-3 μm mass median diameter (50% of droplets less than or equal to 0.1-3 μm)" (see page 297, right column, first full paragraph). Jaffe does not teach or suggest the claimed particle size of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns.

Although Jaffe discloses that IFN-γ can be aerosolized and inhaled while retaining some biologic activity after reaching the lower respiratory tract, Jaffe does not show that the biological activity of the aerosolized γ-IFN is substantially the same as that of the aqueous γ-IFN solution. Further, Jaffe does not show that the molecular size distribution of the aerosolized γ-IFN is substantially the same as that of the aqueous γ-IFN solution.

Accordingly, the 35 U.S.C. 103(a) rejection of Claims 16-23 and 25-28 over Huland and Jaffe in view of Debs, Ruskewicz, Nayar and Hora should be reversed.

C. Rejection as unpatentable under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention.

Claims 16-23 and 25-28 are rejected under 35 U.S.C. 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention. Appellants respectfully traverse the rejection.

The Examiner contends that the terms "biological activity substantially the same" and "molecular size distribution substantially the same" are indefinite for failing to define whether "substantially the same" meant that the biological activity or molecular size distribution was exactly the same or were within some predetermined numerical range. The Examiner suggests a rhetorical example to illustrate the alleged indefiniteness of the phrase "substantially the same." Appellants do not agree that the limitation "substantially the same" is indefinite. A claim limitation employing the term "substantially" has been previously determined not to be indefinite under 35 U.S.C. 112, second paragraph. The court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines contained in the specification. *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The court held that the limitation "which produces substantially equal E and H plane illumination patterns" was definite because one of ordinary skill in the art would know what was meant by "substantially equal." *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988). In both cases, the claim did not need to recite a definitive range of similarity in order to avoid being found unpatentably vague, but instead the claim limitation was to read in light of the general guidelines in the specification and the meaning ascribed to the term "substantially" by one skilled in the art. Here, Appellants have quantitatively demonstrated the substantial retention of γ-IFN

biological activity and γ-IFN molecular size distribution. In view of the general guidelines contained in the specification, a skilled person would know what is meant by "substantially the same" as that of the aqueous γ-IFN solution in Claim 22.

Therefore, the 112, second paragraph rejection of Claims 16-23 and 25-28 should be reversed.

D. Conclusion

For the reasons stated above, the Examiner's rejection of Claims 1-23 and 27-34 is erroneous. The Honorable Board is respectfully requested to reverse the Examiner's rejection of all claims on appeal and remand the application to the Examiner for allowance.

Respectfully submitted,

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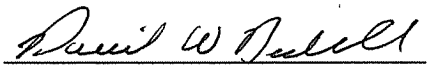

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VIII. CLAIMS APPENDIX

16. The composition of claim 22, wherein said solution contains at least one million International Units of γ-IFN/ml, as measured by (i) the ability of γ-IFN to stimulate CD64 antigen expression in cultured enriched human monocytes, or (ii) the ability of γ-IFN to stimulate HLA-DR antigen expression in cultured human monocytes.

17. The composition of claim 22, wherein said stabilizing agent comprises mannitol.

18. The composition of claim 17, wherein said mannitol is present in an amount between 5-15 mM.

19. The composition of claim 22, wherein said dispersing agent comprises polysorbate.

20. The composition of claim 19, wherein the polysorbate is present in an amount between 50-200 mg/liter weight percent.

21. The composition of claim 22, wherein the aqueous γ-IFN solution has a viscosity at room temperature of less that 2Cp.

22. A liquid-droplet aerosol composition formed from an aqueous γ-IFN solution having a known, γ-IFN biological activity, and comprising a dispersing agent and a stabilizing agent in an amount effective to stabilize the γ-IFN upon aerosolization, wherein the stabilizing agent consists of a sugar, an alcohol, or an amino acid, wherein the liquid-droplet aerosol composition has

(a) defined-size droplet particles in a selected size range selected from the group consisting of (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, and (v) greater than 10 microns;

(b) a γ-IFN biological activity substantially the same as that of the aqueous γ-IFN solution; and

(c) a γ-IFN molecular size distribution substantially the same as that of the aqueous γ-IFN solution.

23. The composition of claim 22, wherein at least 95% of the droplet particles have a size in the selected size range.

25. The composition of claim 22, wherein at least 80% of the droplet particles have a size in the selected size range.

26. The composition of claim 22, which are formed by placing the aqueous γ-IFN solution against a plate having defined-size openings or pores, and forcing the aqueous γ-IFN solution through the openings or pores.

27. The composition of claim 22, wherein the selected size range is 3-5 microns.

28. The composition of claim 22, wherein the selected size range is 5-10 microns.

IX. EVIDENCE APPENDIX

-- NONE --

X. RELATED PROCEEDINGS APPENDIX

-- NONE --